REMARKS

Claims 1, 34-39, 41, and 42 are pending in this application. Claims 38 and 41 have been withdrawn from consideration by the Examiner. Claims 1, 34-37, 39, and 42 have been amended.

In accordance with 37 C.F.R. §1.121, a marked up copy of the presently amended specification paragraphs and claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing. Furthermore, to ensure that Applicants' pending claims match those of the Patent Office, a clean copy of the entire set of pending claims is also appended hereto.

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

1. having been altered in any way for any reason related to patentability;

2. having been narrowed;

3. a concession that the invention as patented does not reach as far as the original, unamended claim;

4. a surrender of any subject matter as a condition of receiving a patent; and/or,

5. estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

All of the remaining pending claims 1, 34-37, 39, and 42 stand rejected.

The 35 U.S.C. § 102 Rejection

The Examiner has rejected Claim 1 as anticipated by JP 51105093, JP 53044591, or JP 52023094. The Examiner believes Claim 1 is anticipated by these references because he finds that:

> the "group" renders the term open-ended, in that the claim language would cover any moiety with a heterocyclic ring present, even if not every atom were in that ring. It is not clear what else could be present. That is, heterocyclic group could cover a situation where X, Y and the C-N part of the purine formed –J-Heterocyclic, where J is some unspecified linker, because the –J-Heterocyclic is still a heterocyclic group, albeit not 100% heterocyclic. Similarly, the ring could have any substituent, as such a group would still be a heterocyclic group. (Office Action p. 4)

In particular, the Examiner points to the two compounds in the first column of p. 706, in JP 51105093; the second species in the second column of p. 779, in JP 53044591; and the compound in the first column of p. 929, in JP 52023094.

As to the second compound on p. 706, in JP 51105093, it cannot anticipate any of the compounds of formula 1 of the current invention. The compounds of the current invention do not allow for a link between an R' and the X group, which is seen in the second compound on p. 706.

As to the other compounds cited by the Examiner, they cannot anticipate any of the compounds of formula 1 of this invention. No matter what cyclic group forms when X and Y are taken together to form a cyclic group, there must still be a direct linkage from the P(O) to the C of the purine ring. These other compounds have no such direct linkage.

In addition, the compounds cited by the Examiner are not of the type where there is a P(O)–X linkage, and X and Y are taken together to form a cyclic group. The compounds cited by the examiner have a P(O)–O–CH_2–X type linkage. In other words, there is an oxygen atom and a methylene group between the P and the X that forms some sort of convoluted cyclic linkage with Y. The O–CH_2 cannot be part of X, because it is not part of any ring.

The Applicants believe that the Examiner finds these compounds to anticipate the current invention, because he finds the claim language indefinite. The Examiner's indefiniteness rejection is discussed in more detail below. However, the claim language when read in light of

the specification cannot support a definition where these cited compounds would fall under the scope of Claim 1.

In view of this, the Applicants respectfully request that the Examiner withdraw the rejection that Claim 1 is anticipated.

The 35 U.S.C. § 112 Rejections

Claims 1, 34-37, 39, and 42 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for particularly pointing out and distinctly claiming the subject matter which the applicant regards as the invention. The Applicants respectfully traverse this rejection.

Claim 36 stands rejected, because the Examiner contends that the scope of the claim is unknown, because "who is actually in need thereof" involves extensive and potentially open-ended research. The Examiner says:

> Which diseases are these? Determining who is in need thereof requires knowing which disease is to be treated. Does the person have to actually have a disease? That is, does this claim cover giving the drug to someone who is healthy?
>
> If not, determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one conclude that Disease D does not fall within this claim? (Office Action p. 3)

The Examiner also urges the Applicants to keep in mind that:

> A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?
>
> B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital – should the drug be given e.g. once a day, or four times in divided dosages? Thus, now many dosages or dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?
>
> C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need to be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? (Office Action p. 3)

The Applicants respectfully note that the specification distinctly points out who may be "in need thereof" FBPase inhibitors to inhibit FBPase at AMP site. At page 6 of the specification, it says that these inhibitors can be used in "treatment or prevention of diseases responsive to inhibition of gluconeogenesis and in diseases responsive to lowered blood glucose levels." (*see* p. 6, lines 18-21). In addition the utility of these inhibitors is again pointed out in the specification on page 61, lines 15-32, where it is disclosed that "FBPase inhibitors at the AMP site may be used to treat diabetes mellitus, lower blood glucose levels, and inhibit gluconeogenesis." Also disclosed are additional utilities in lines 17-18 "(t)o treat excess glycogen storage diseases and in lines 23-24, "(t)o treat or prevent diseases associated with increased insulin levels." Furthermore it is given that "Increased insulin levels are associated with an increased risk of cardiovascular complications and atherosclerosis." In light of the specification, the Applicants believe that a person of ordinary skill in the art would understand who is "in need thereof."

In addition, in *Ex parte Skuballa*, the Board stated that a claim "(i)s not rendered indefinite because it recites diverse utilities." *Ex parte Skuballa*, 12 USPQ2d 1570, 1571 (Bd. Pat. App. & Int. 1989). The Board further stated "We are satisfied that the skilled worker in this art could readily optimize effective dosages and administration regimens for each of the recited utilities." *Id.* In *Ex parte Cole, Howarth, and Reading*, the Board said that "We know of no statutory or case law requiring each and every compound within a claim to be equally useful for each and every contemplated application." *Ex parte Cole, Howarth, and Reading*, 223 USPQ 94,

95 (Bd. Pat. App. & Int. 1983). The Board went on to say: "Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination." *Id.* at 95-96 (internal citations omitted). Thus, the Applicants believe that one skilled in the art would be able to ascertain those patients that would be in need thereof of the use of the novel FBPase inhibitors.

The Examiner also appears to be concerned about dose issues. Claim 36 clearly calls for "administering to said patients an FBPase inhibitory amount of a compound of formula (1)." This claim is similar to claims in *Ex parte Skuballa.* In that case, the examiner found that method of treatment claims which recited an "effective amount of a compound" were indefinite. *Ex parte Skuballa*, 12 USPQ2d at 1571. The Board declined to agree with the examiner, saying "We are unable to subscribe to the examiner's contention particularly as to the method of use claims, namely claims 20 and 21 which set forth the function or functions to be achieved by administering the claimed 5-cyanoprostacyclin compounds to the patient." *Id.*
The Board also found: "As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures." *Id.*
Furthermore the Board stated that "While some experimentation may be required to determine optimum dosages.....to achieve a particular biological response, such experimentation is not considered to be undue." *Id.*

Just as in *Ex parte Skuballa*, claim 36 clearly sets forth the function to be achieved by administering compounds of formula (1). A person of ordinary skill in the art could easily determine the appropriate doses.

Therefore, Applicants respectfully request the withdrawal of the rejection that Claim 36 is indefinite.

Claims 1, 34-37, 39, and 42 stand rejected for three reasons. The Examiner lists them as follows:

1. X combined with Y to form the group of "cyclic alkyl" is impossible. First, alkyl by its very nature is not cyclic. It is possible that applicants intend "cycloalkyl" but that

is also impossible, because the Y is attached to the N, meaning that the N will be in the ring.

2. "Heterocyclic" is indefinite. What is the size of the ring? What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423.

3. Further, the "group" renders the term open-ended, in that the claim language would cover any moiety with a heterocyclic ring present, even if not every atom were in that ring. It is not clear what else could be present. That is, heterocyclic group could cover a situation where X, Y and the C-N part of the purine formed –J-Heterocyclic, where J is some unspecified linker, because the –J-Heterocyclic is still a heterocyclic group, albeit not 100% heterocyclic. Similarly, the ring could have any substituent, as such a group would still be a heterocyclic group. (Office Action p. 4)

Reason 1:

The Examiner is correct that whatever cyclic group that is formed will include the N as part of the ring. As such, the group that forms cannot properly be termed a cyclic alkyl. Therefore, the Applicants have amended all of the claims to eliminate this particular use of the term "cyclic alkyl" from the claims.

Reason 2:

The Applicants note that the term "heterocyclic" is defined at p. 9 of the specification as:

> The term "heterocyclic" and "heterocyclic alkyl" refer to cyclic alkyl groups containing at least one heteroatom. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a heteroatom or through a carbon atom in the ring.

In addition the specification at p. 9 also defines the term "cyclic alkyl" and "alkyl" as:

> The term "cyclic alkyl" refers to alkyl groups that are cyclic.
>
> The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups. Alkyl groups may be optionally substituted.

According to MPEP § 2173.02, the definiteness of claim language must not be analyzed in a vacuum, but in light of:

> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Applicants believe that a person of ordinary skill in the are would understand what is meant by the term "heterocyclic" as used in the pending claims. As stated in the specification, it is a cyclic alkyl group containing at least one heteroatom. In addition, the Board in *Ex parte Scherberich* said that the term heterocyclic "is seen as having an art recognized meaning." *See Ex parte Scherberich*, 201 USPQ 397, 399 (Bd. Pat. App. & Int. 1977). This especially true here where the specification gives additional guidance to one skilled in the art.

Even if the Examiner considers the term "heterocyclic" to be somewhat broad, there is nothing inherently wrong with a broad claim. *See* MPEP 2173.04. According to MPEP 2173.04, "if the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from what is defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph." *In re Wiggins* is distinguishable on this basis, because there the applicant apparently intended the invention of be of a different scope from what was defined in the claims. *See In re Wiggins*, 179 USPQ 421, 424 (C.C.P.A. 1973). The court stated that the applicants could have employed more precise language based on the specification. *See Id.* Here, the Applicants have not otherwise indicated that they intend the invention to be of a scope different from what is defined in the claims.

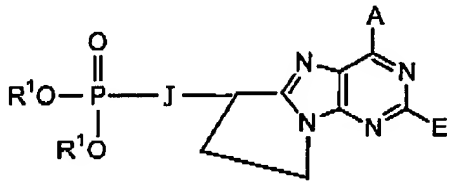
Reason 3:

The Applicants are unsure as to why the Examiner finds the term "group" to be indefinite. The term group is used throughout the specification to refer to molecules that share a particular feature. As stated above, the specification defines the term heterocyclic as:

> The term "heterocyclic" and "heterocyclic alkyl" refer to cyclic alkyl groups containing at least one heteroatom. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a heteroatom or through a carbon atom in the ring. p. 9

There is nothing in this definition that would indicate that a "heterocyclic group could cover a situation where X, Y and the C-N part of the purine formed –J-Heterocyclic, where J is some unspecified linker."

The Applicants believe the Examiner means something like the figure below.



J is clearly not part of the heterocyclic group, it is merely attached to the heterocyclic group. If the Applicants intended to cover this compound, then J would have to be included in formula 1, and it is not.

Therefore, the Applicants respectfully request the withdrawal of the rejection that Claims 1, 34-37, 39, and 42 are indefinite.

Conclusion

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

Respectfully Submitted,

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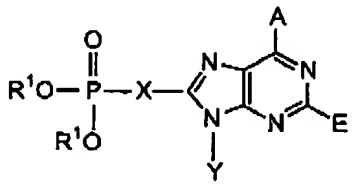
MARKED UP VERSION OF THE CLAIMS

Pending Claims in 0014DIV1

1. (Twice Amended) A compound of formula 1:



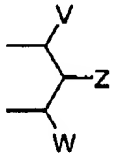
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy,

alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

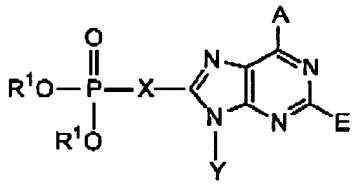
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

34. (Twice Amended) A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula (1):



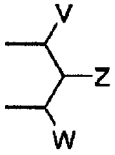
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

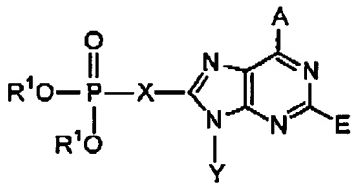
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

35. (Twice Amended) A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula (1):



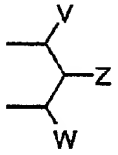
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

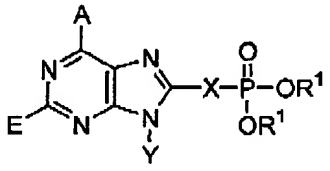
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

36. (Twice Amended) A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula (1):



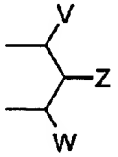
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-R^3, $-C(R^2)_2$-OC (O)R^3, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

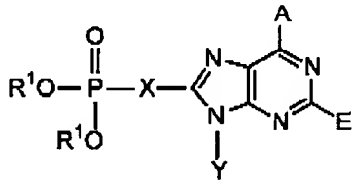
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

37. (Twice Amended) A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula (1):



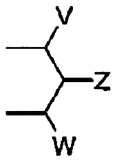
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-R^3, $-C(R^2)_2$-OC (O)R^3, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

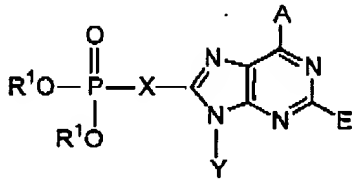
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

39. (Twice Amended) A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor wherein said inhibitor is a compound of formula (1):



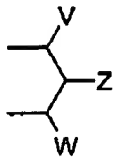
wherein

A is selected from the group consisting of $-NR^8{}_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7{}_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2$-OC (O)R^3, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

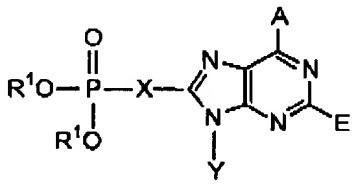
R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.

42. (Twice Amended) A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor, wherein said inhibitor is a compound of formula (1):



wherein

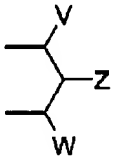
A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^7_2$;

X together with Y forms a cyclic group selected from the group of [cyclic alkyl,] heterocyclic, and aryl;

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$-aryl, –alk-aryl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2$-C(O)-R^3, $-C(R^2)_2$-OC (O)R^3, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, –alk-S-C(O)R^3, –alk-S-S-alkylhydroxy, and –alk-S-S-S-alkylhydroxy, or

together R^1 and R^1 are –alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2_2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH{=}CR^2R^2)OH$, $-CH(C{\equiv}CR^2)OH$, and $-R^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

pharmaceutically acceptable prodrugs and salts thereof.